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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Medical Officer Review

BLA STN #:	103795/5034
Date Received by CBER:	July 16, 2001
Established and Proprietary Product Names:	Etanercept (Enbrel)
Applicant:	Immunex Corporation
Indication or change being requested:	New indication for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis
Reviewer Name and Mail Code:	Jeffrey Siegel, M.D., HFM-582
Date Review Completed:	January 15, 2002

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I. Background

A. Psoriatic arthritis

Psoriatic arthritis is a chronic inflammatory arthritis seen in patients with psoriatic skin lesions that is distinct from other forms of arthritis such as rheumatoid arthritis and osteoarthritis.[1] It is characterized by a variable pattern of joint involvement. Approximately 95% of patients with psoriatic arthritis have involvement of the peripheral joints, of whom the majority have at least 5 involved joints. Some patients have a pauciarticular form of arthritis. Some have exclusively DIP (distal interphalangeal joint) involvement, in contrast to RA, which is characterized by PIP (proximal interphalangeal joint) involvement. Approximately 5% have exclusively spinal involvement similar to ankylosing spondylitis, while 20-50% have involvement of both the spine and peripheral joints.

A diagnosis of psoriatic arthritis requires evidence of the skin or nail changes characteristic of psoriasis. In contrast to RA, where a female preponderance is seen, men and women are represented roughly equally among patients with psoriatic arthritis. The disease is rare under the age of 13, and the usual age of onset is 30-50 years of age. Psoriatic arthritis is associated with inflammation of the joints and spine, but also of the periosteum, along tendons and at tendon insertion pints, a phenomenon known as ensethopathy. Like rheumatoid arthritis, structural damage to joints can be visualized by radiographic imaging. However, the types of radiographic changes are different. Erosions of the DIPs are seen, which may evolve in severe cases into terminal whittling of the proximal bone, termed pencil-in-cup deformities. Some studies suggest that the long-term outcome of psoriatic arthritis is better than rheumatoid arthritis. However, joint damage is still significant. One longitudinal study showed the proportion of patients with 5 or more damaged joints increased from 19% to 41% over a 5-year time span.[2]

Currently, rheumatologists treat patients with psoriatic arthritis with similar modalities as those used in rheumatoid arthritis, such as NSAIDs, corticosteroids, exercise, physical therapy and education. Suppression of skin disease is believed to improve the joint manifestations. Finally, DMARDs are used in patients with progressive polyarticular

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[1] Vasey, FB: Psoriatic Arthritis, Primer on the Rheumatic Diseases, 10th ed. Edited by Schumacher, HR, Jr, Klippel, JH and Koopman WJ, Atlanta, Arthritis Foundation, 1993, pp 161-163

[2] Gladman DD, Stafford-Brady F, Chi-Hsing C: Longitudinal study of clinical and radiological progression in psoriatic arthritis. J Rheumatol 17:809-12, 1990

disease, including methotrexate, gold, hydroxychloroquine, sulfasalazine. No DMARDs are currently approved for treatment of psoriatic arthritis.

B. Regulatory history

As stated above no disease modifying agents are currently approved for the treatment of psoriatic arthritis. In addition, no FDA guidance document has been issued for psoriatic arthritis. The sponsor approached the agency in 1999 about extending the indication of etanercept to psoriatic arthritis, based on a single-center phase 2 study (study 16.0612) that suggested biologic activity. The agency requested that additional data be submitted, preferably from a multi-center study, to reproduce the results and to provide additional safety and efficacy information.

No single assessment tool has been fully validated in clinical trials of psoriatic arthritis. A variety of primary endpoints were considered for the phase 3 trial of etanercept, including the PsARC and the ACR20, both of which measure success or failure based on a set of response criteria. The PsARC, which was the primary endpoint for the phase 2 study, defines a treatment response as an improvement in 2 or more of the following 4 measures: patient global, physician global, tender/painful joint scores and swollen joint scores. The ACR20 response criteria were developed and validated to assess responses to treatment in patients with rheumatoid arthritis. The ACR20 includes variants of the same 4 measures as the PsARC, as well as a measure assessing pain, a questionnaire assessing function/disability and a laboratory measure of acute phase reactants. It was decided that the ACR20 would be the primary endpoint and the PsARC a secondary endpoint for the phase 3 trial (study 16.0030).

C. Response to vaccination in patients receiving etanercept

As part of the initial approval of Enbrel, Immunex agreed to carry out post-marketing studies to determine the effects of etanercept on B cell function. In a previous submission, Immunex submitted open-label data on a limited number of etanercept-treated patients vaccinated with [redacted] vaccine and pneumococcal vaccine who were compared to historical controls. As part of an ongoing open-label safety trial (16.0018) of Enbrel in rheumatoid arthritis, 17 subjects from two sites were recruited for this substudy. Serum samples were drawn prior to and 28 days following administration of both [redacted] and pneumococcal vaccines. IgG antibody concentrations to pneumococcal antigens were measured by [redacted] The [redacted] test was used for measurement of [redacted] antigens.

For the pneumococcal vaccine, an adequate response was defined as a two-fold increase in titer above baseline or a titer of at least [redacted] mcg/ml in [redacted]% of subjects. For the [redacted] vaccine, a [redacted] fold increase in titer was defined as an adequate response.

[redacted]

[redacted]

Twelve of 17 (71%) subjects had a 2-fold increase in antibody levels to at least 1 of the 6 pneumococcal antigens measured. All subjects had a post-vaccination antibody level of [redacted] mg/ml or greater to at least one of the 6 antigens. All subjects met the prespecified criteria of a 2-fold rise in antibody levels or a final level of at least [redacted] mg/ml.

These data suggested that etanercept use was not associated with any gross abnormalities in B cell function. However, conclusions from the study were limited by the lack of concurrent controls and by the small size of the study. To obtain additional data from a controlled trial of the effects of etanercept on B cell function, Immunex added to the phase 3 trial of etanercept for psoriatic arthritis (16.0030) an assessment of responses to pneumococcal polysaccharide vaccine.

II. Study 16.0030

Study 16.0030 was a double-blind, randomized, placebo-controlled, phase 3 study of etanercept 25 mg or placebo sc biw for 24 weeks in patients with active psoriatic arthritis. The study was carried out at 17 sites in the U.S. Patients were required to have plaque psoriasis with a target skin lesion of 2 cm diameter or greater that was stable, i.e. not accelerating. Patients were required to have arthritis with at least 3 swollen and 3 tender/painful joints. Patients had at least one of the following subtypes of psoriatic arthritis:

- DIP involvement
- Polyarticular arthritis (no rheumatoid nodules)
- Arthritis mutilans
- Asymmetric peripheral arthritis
- Ankylosing spondylitis-like

Patients were required to have had an inadequate response to NSAIDs. Patients could continue on stable doses of corticosteroids, NSAIDs and topical therapies to the scalp, axillae and groin. Patients receiving MTX were allowed to continue on stable doses. Other DMARDs besides MTX were not allowed for 4 weeks before beginning study drug or during the study. Recent PUVA or UVB within the previous 2-4 weeks was not allowed. Patients with guttate or pustular psoriasis were excluded.

Patients had assessments of their disease activity at 4, 12 and 24 weeks. Joint scores and counts were determined by independent, blinded joint assessors. No adjustments to anti-rheumatic therapy were allowed during the 6 months of the trial, but patients with demonstrated lack of efficacy were discontinued from study drug after the primary endpoint assessment at 3 months. Lack of efficacy was defined as patients who met all of the following criteria:

- Patient global assessment was not improved over baseline or patient global increased by 2 or more points compared to the best level during the study;
- A 20% or greater worsening in either the painful/tender joint count or the swollen joint count compared to the best joint evaluation OR no more than a 10% improvement compared to baseline at any time during the study;
- The previous 2 criteria necessitated a change in anti-rheumatic therapy

Patients who discontinued study drug were encouraged to return for their full 6-month evaluations.

The primary endpoint of the study was the proportion of subjects who achieved an improvement at 3 months as assessed by the American College of Rheumatology definition of improvement in rheumatoid arthritis (ACR20). A subject with improvement in the ACR20 is defined as achieving at least a 20% improvement in tender joint count and swollen joint count, as well as a 20% or greater improvement in three of the following five parameters: patient global assessment (by [redacted] physician global assessment [redacted], pain [redacted], disability (health assessment questionnaire or HAQ) and acute phase reactant. Patients discontinuing for lack of efficacy who met the above prespecified criteria were considered non-responders.

The randomization was blocked and stratified by concomitant MTX use. The primary analysis was the Cochran-Mantel-Haenszel test stratified by MTX use. A [redacted] Secondary psoriatic arthritis endpoints include the ACR20 at 6 months, the psoriatic arthritis response criteria (PsARC) at 3 and 6 months. A responder for the PsARC is defined as a decrease by [redacted] or greater in at least 2 of the following 4 parameters: patient global, physician global, tender joint score and swollen joint score.

The psoriasis endpoints for the study were all considered to be secondary endpoints. These endpoints consisted of the response of the target lesion to therapy at 12 and 24 weeks, the Dermatologists Static Global Assessment (DSGA) of Target Lesion and overall psoriasis score distribution, the Psoriasis Area and Severity Index (PASI) scores at 12 and 24 weeks for the subset of patients with at least 3% of body surface area (BSA) involved at baseline. The response of the target lesion was assessed based on plaque elevation (0-4 scale), scaling (0-4 scale) and erythema (0-4 scale). The percent reduction from baseline was assessed as well as a categorical endpoint assessing the percentage of patients achieving a 50, 75 and 90% improvement from baseline. The Dermatologists Static Global Assessment of Target Lesion score distribution was assessed based on a 0-5 scale (clear to severe lesion). The distribution of scores was assessed as well as the proportion of patients with a rating of clear and almost clear (0 and 1).

A. Study conduct

At least 95% of subjects who enrolled in each of the study arms continued in the study taking study drug until the time of assessment of the primary endpoint at 12 weeks (Table

1). One subject discontinued study drug before 12 weeks in the etanercept arm, compared to 5 in the placebo arm. The difference was due to a higher number discontinuing due to lack of efficacy (2 in the placebo arm vs. 0 in the etanercept arm) and patient refusal (also 2 in the placebo arm vs. 0 in the etanercept arm). A higher proportion of subjects continued 24 weeks of blinded study drug in the etanercept arm compared to placebo (98% vs. 88%). The main reasons for the higher discontinuation rate in the placebo arm were lack of efficacy (23 in the placebo arm vs. 5 with etanercept) and patient refusal (4 patients vs. 1). A single patient dropped out in the etanercept group due to toxicity.

Table 1: Subject disposition

	Placebo	**Etanercept**
	(N = 104)	(N = 101)
Patient Status	n (%)	n (%)
Completed 12 weeks in study	102 (98)	100 (100)
Completed 12 weeks on study drug	99 (95)	100 (99)
Discontinued study drug due to:		
Lack of efficacy (LOE)	2 (2)	0
Lost to follow-up	1 (1)	1 (1)
Patient refusal	2 (2)	0
Completed 24 weeks in study	92 (88)	99 (98)
Completed 24 weeks on study drug	72 (69)	93 (92)
Discontinued study drug due to:		
Death	1 (1)	0
Adverse event	1 (1)	1 (1)
Lack of efficacy (LOE)	23 (22)	5 (5)
Lost to follow-up	3 (3)	1 (1)
Patient refusal	4 (4)	1 (1)

A small number of protocol violations took place during the trial. There were 7 subjects who were assigned to the incorrect stratum concerning MTX use. There were similar numbers in each study arm. In each case, the subject was analyzed based on the stratum that they were randomized in. One patient in the etanercept arm received an oral corticosteroid pulse for chest wall pain before the primary endpoint assessment. That patient was considered a non-responder. Finally, one placebo patient was given etanercept by mistake. That patient was included in the placebo group for analysis.

Regarding compliance with blinded study medication, approximately 90% of the patients who continued in the study missed no more than 1 dose at 3 months. Eighty-seven percent of patients in the placebo arm and 90% of subjects in the etanercept arm missed no more than 2 doses at 6 months.

B. Baseline characteristics

The baseline characteristics of the study subjects is shown in Table 2. The mean age was approximately 47, with about equal representation of men and women. The patients had long-standing disease with a mean duration of psoriasis of approximately 19 years and a mean duration of psoriatic arthritis of approximately 9 years. Approximately 60% of subjects had a large enough body surface area involved with psoriasis to qualify for evaluation of the PASI results. Approximately half the subjects were receiving concomitant methotrexate. Each of the subtypes of psoriatic arthritis were represented in the study. However, only 7 were enrolled with the ankylosing spondylitis-like subtype and only 3 with the arthritis mutilans subtype. No major imbalances were noted between study arms, although slightly more males were enrolled in the etanercept arm.

Table 2: Baseline demographics

	Placebo	**Etanercept**
Characteristic	N = 104	N = 101
Mean age in years	47.3	47.6
(range)	(21 – 73)	(18 – 76)
Male (n [%])	47 (45)	58 (57)
Race (n [%]):		
Caucasian	95 (91)	91 (90)
Hispanic	5 (5)	6 (6)
Black	2 (2)	3 (3)
Other	2 (2)	1 (1)
Mean weight (kg)	88.4	91.5
Duration of PsA in years (mean)	9.2	9.0
Duration of psoriasis in years (mean)	19.7	18.3
Mean psoriasis BSA (%)	10.2	10.9
(range)	(1.0 – 90.0)	(0.5 – 80.0)
Evaluable for PASI results (n [%])	62 (60)	66 (65)
No. of prior DMARDs (mean)	1.6	1.7
Concomitant therapy during study (n [%]):		
Corticosteroids	16 (15)	19 (19)
NSAIDs	86 (83)	89 (88)
Methotrexate	51 (49)	45 (45)
Subtypes of psoriatic arthritis (n [%]): *		
DIP joints of hand and feet	52 (50)	52 (51)
Arthritis mutilans	2 (2)	1 (1)
Polyarticular arthritis	86 (83)	87 (86)
Asymmetric peripheral arthritis	40 (38)	41 (41)
Ankylosing spondylitis-like	4 (4)	3 (3)

* Some patients were noted to have more than one subtype of PsA.

The patients had active psoriatic arthritis at baseline, as shown in Table 3. Mean tender joint counts were approximately 21 and mean swollen joint counts were approximately 13. There were no major imbalances across study arms.

Table 3: Baseline disease activity

	Placebo	**Etanercept**
	N = 104 mean (median)	N = 101 mean (median)
Tender joint count [a]	22.1 (17.0)	20.4 (18.0)
Tender joint score [b]	31.1 (21.0)	27.5 (22.0)
Swollen joint count [c]	15.3 (12.5)	15.9 (13.0)
Swollen joint score [d]	20.6 (14.5)	22.5 (15.0)
Physician global assessment [e]	2.9 (3.0)	2.9 (3.0)
Patient global assessment [e]	3.0 (3.0)	3.0 (3.0)
Morning stiffness (minutes)	126.8 (60)	118.9 (60)
Pain assessment [e]	3.0 (3.0)	3.0 (3.0)
Disability index (HAQ) [f]	1.1 (1.0)	1.1 (1.1)
CRP [g]	1.7 (1.1)	2.2 (1.6)

a Scale 0 – 78
b Sum of 78 joint pain/tenderness scores measured on a 4-point scale
c Scale 0 – 76
d Sum of 76 joint swelling scores measured on a 4-point scale
e 0 = best, 5 = worst (Likert scale)
f 0 = best, 3 = worst
g Normal range: 0 – 0.79 mg/dL

C. Efficacy analysis

The primary endpoint for the study was the proportion of patients achieving an ACR20 response at 12 weeks. Fifty-nine percent of patients in the etanercept arm met the primary endpoint as compared to 15% of patients in the placebo arm (Table 4). The results were highly significant, with a p value of <0.001. Responses were rapid with differences appearing by 4 weeks (Table 5). Higher levels of response were also observed, with approximately 38% of etanercept-treated patients achieving a 50% improvement at 6 months and approximately 10% achieving a 70% improvement. The proportion of patients achieving a response appeared to reach a plateau at 3 months, as results at 6 months were no higher than those observed at 3 months.

Table 4: Primary psoriatic arthritis endpoint: Number (%) achieving ACR 20 response at week 12

Parameter	Placebo N = 104 n (%)	Etanercept N = 101 n (%)	p value*
ACR 20 at 12 weeks	16 (15)	60 (59)	< 0.001

* p value determined by Cochran-Mantel-Haenszel row means test

Table 5: Time course of ACR 20, 50 and 70 responses

	Placebo	Etanercept	
	N = 104	N = 101	
Parameter	n (%)	n (%)	p value
ACR 20			
4 weeks	11 (11)	38 (38)	< 0.001 *
12 weeks	16 (15)	60 (59)	< 0.001 *
24 weeks	14 (13)	50 (50)	< 0.001 *
ACR 50			
4 weeks	2 (2)	11 (11)	0.009 *
12 weeks	4 (4)	38 (38)	< 0.001 *
24 weeks	4 (4)	37 (37)	< 0.001 *
ACR 70			
4 weeks	0	1 (1)	0.493 †
12 weeks	0	11 (11)	< 0.001 †
24 weeks	1 (1)	9 (9)	0.009 †

* p values determined by Cochran-Mantel-Haenszel row means test
† p values determined by Fisher's exact test

Improvement was also observed in etanercept-treated patients as assessed by the PsARC response criteria (Table 6). A somewhat higher proportion of patients achieved PsARC criteria at 3 months, compared to the ACR20 (72% vs. 59%), but the proportion achieving PsARC criteria in the placebo group was also higher (31% vs. 15%).

Table 6: Number (%) achieving PsARC over time

	Placebo	Etanercept	
	N = 104	N = 101	
Achieved PsARC	n (%)	n (%)	p value*
4 weeks	25 (24)	57 (56)	< 0.001
12 weeks	32 (31)	73 (72)	< 0.001
24 weeks	24 (23)	71 (70)	< 0.001

* p values determined by Cochran-Mantel-Haenszel row means test

Each of the components of the ACR20 showed greater improvement among etanercept-treated patients (Table 7 and Table 8) than in controls. The median swollen joint count fell by 61% and the tender joint count, physician and patient global assessment, pain assessment and CRP levels all fell by at least two-thirds. In contrast, among controls, there was no change in the median physician or patient global assessment, pain assessment or CRP levels during the 6 months of the trial.

HAQ disability scores fell from a median baseline level of 1.1 to 0.3 in the etanercept group, representing a 58% improvement compared to no improvement in the median HAQ scores among controls. In addition, more patients attained high levels of improvement in the HAQ in the etanercept-treated group than in controls. Half the patients had an improvement of 0.5 units or more, compared to 14% among controls and 23% of etanercept-treated patients had an improvement of 1.0 units or greater, compared to 5% among controls.

Table 7: Components of ACR and assessment of morning stiffness

	Placebo	**Etanercept**
	N = 104	N = 101
Parameter	mean (median)	mean (median)
Tender joint count: [a]		
Baseline	22.1 (17.0)	20.4 (18.0)
4 weeks	18.8 (15.0)	13.3 (11.0)
12 weeks	18.3 (13.5)	8.8 (5.0)
24 weeks	17.7 (13.0)	9.2 (5.0)
Swollen joint count: [b]		
Baseline	15.3 (12.5)	15.9 (13.0)
4 weeks	13.3 (11.5)	12.1 (11.0)
12 weeks	12.8 (12.0)	8.1 (5.0)
24 weeks	11.5 (9.5)	7.2 (5.0)
Physician global assessment: [c]		
Baseline	2.9 (3.0)	2.9 (3.0)
4 weeks	2.6 (3.0)	1.8 (1.0)
12 weeks	2.8 (3.0)	1.5 (1.0)
24 weeks	2.7 (3.0)	1.4 (1.0)
Patient global assessment: [c]		
Baseline	3.0 (3.0)	3.0 (3.0)
4 weeks	2.8 (3.0)	2.2 (2.0)
12 weeks	2.8 (3.0)	1.8 (1.0)
24 weeks	2.9 (3.0)	1.7 (1.0)
Morning stiffness (minutes):		
Baseline	126.8 (60.0)	118.9 (60.0)
4 weeks	109.6 (60.0)	86.6 (20.0)
12 weeks	124.1 (60.0)	69.1 (15.0)
24 weeks	131.8 (60.0)	64.0 (15.0)
Pain assessment: [c]		
Baseline	3.0 (3.0)	3.0 (3.0)
4 weeks	2.8 (3.0)	2.0 (2.0)
12 weeks	2.8 (3.0)	1.6 (1.0)
24 weeks	2.8 (3.0)	1.6 (1.0)
CRP [d]		
Baseline	1.7 (1.1)	2.2 (1.6)
4 weeks	1.8 (1.1)	0.5 (0.2)
12 weeks	1.8 (1.2)	0.5 (0.2)
24 weeks	1.6 (1.1)	0.4 (0.2)

a Scale 0 – 78
b Scale 0 – 76
c 0 = best, 5 = worst (Likert scale)
d Normal range: 0 – 0.79 mg/dL

Table 8: HAQ (Health Assessment Questionnaire) scores

	Placebo	Etanercept	
	N = 104	N = 101	
Parameter	mean (median)	mean (median)	p value
Actual values: *			
Baseline	1.1 (1.0)	1.1 (1.1)	
4 weeks	1.0 (1.0)	0.7 (0.6)	
12 weeks	1.0 (1.0)	0.6 (0.4)	
24 weeks	1.0 (0.9)	0.5 (0.3)	
Percent change from baseline:			
4 weeks	8.0 (9.1)	35.1 (29.7)	< 0.001 †
12 weeks	6.3 (0)	53.5 (63.1)	< 0.001 †
24 weeks	6.4 (0)	53.6 (57.7)	< 0.001 †
Number (%) of patients with significant improvements in HAQ scores at 24 weeks:	n (%)	n (%)	
HAQ score ≤ 0.5	30 (29)	61 (60)	< 0.001 ‡
HAQ improved ≥ 0.5 unit	15 (14)	51 (50)	< 0.001 ‡
HAQ improved ≥ 1.0 unit	5 (5)	23 (23)	< 0.001 ‡

* 0 = best; 3 = worst

† p values determined by 2-sided Wilcoxon rank sum test

‡ p values determined by Cochran-Mantel-Haenszel row means test

Table 9 shows the proportion of patients who had normalization of individual disease activity measures, as assessed by patients with the best possible value at 24 weeks, or to a value of no higher than the upper limit of normal in the case of the CRP. Eight-eight percent of etanercept-treated patients had normalization of their CRP levels, compared to 38% in the placebo arm. With respect to the clinical outcomes, more than one-third of all subjects in the etanercept arm had no disability at six months and approximately 30% had no morning stiffness. One-fifth or more of etanercept-treated subjects reported no pain and similar numbers had no tender joints or swollen joints at 6 months. In contrast, fewer than 8% of control subjects had normalization of these clinical measures.

Table 9: Number (%) of patients with normalization of disease activity measures

	Placebo	**Etanercept**
	N = 104	N = 101
Parameter (actual value)	n (%)	n (%)
Tender joint count (none)	2 (2)	23 (23)
Swollen joint count (none)	5 (5)	20 (20)
Physician global assessment (0)	4 (4)	15 (15)
Patient global assessment (0)	1 (1)	13 (13)
Morning stiffness (none)	7 (7)	31 (31)
Pain assessment (none)	3 (3)	21 (21)
Disability index (HAQ) (0)	7 (7)	38 (38)
CRP (≤ upper limit of normal)	40 (38)	89 (88)

1. *Subset analyses*

When patients were subsetted based on their form of psoriatic arthritis, a higher frequency of responses was seen in the etanercept-treated group than in controls for each of the subtypes (**Table 10**). Of note, too few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes to reach robust conclusions. It should also be noted that for the patients with ankylosing spondylitis-like psoriatic arthritis, that it was the peripheral arthritis and not the axial arthritis that was assessed in this study. In addition, patients with purely axial disease were not enrolled as peripheral arthritis was an inclusion criterion.

Table 10: ACR responses, subsetted by subtype of psoriatic arthritis

	Placebo	Etanercept	
	N = 104	N = 101	
ACR 20 at 12 weeks	n (%)	n (%)	p value
Subtype of psoriatic arthritis: *			
	(n = 52)	(n = 52)	
DIP joints of hand and feet	8 (15)	30 (58)	< 0.001 †
	(n =2)	(n = 1)	
Arthritis mutilans	0	1 (100)	0.333 ‡
	(n = 86)	(n = 87)	
Polyarticular arthritis	13 (15)	52 (60)	< 0.001 †
	(n = 40)	(n = 41)	
Asymmetric peripheral arthritis	5 (13)	28 (68)	< 0.001 †
	(n = 4)	(n = 3)	
Ankylosing spondylitis-like	1 (25)	2 (67)	0.486 ‡

* Some patients were noted to have more than one subtype of PsA.
† p values determined by Cochran-Mantel-Haenszel row means test
‡ p values determined by Fisher's exact test

Responses were also assessed in relation to baseline demographics. Ninety-four percent of all patients were younger than 65 year old. Of the 13 patients at least 65 year old, 38% of the etanercept-treated patients and 20% of placebo-treated patients had an ACR20

response at 6 months. Higher response rates were observed among etanercept-treated patients for both men and women (**Figure 1**). Analysis of patients subsetted by ethnicity was limited by the fact that over 90% of patients enrolled in the study were Caucasian. However, 10 Hispanic patients were enrolled, of whom 5 of 6 had a response in the etanercept group, compared to 0/5 in the placebo group. Eight patients enrolled who were neither Caucasian nor Hispanic. Of these, 3 of 4 responded in the etanercept group, compared to 0 of 4 with placebo. An analysis was carried out subsetting patients by study center. Fourteen of the 17 centers enrolled at least 5 subjects and had at least 1 patient enrolled in each study arm. Of these 14, numerically higher response rates were seen among etanercept-treated patients in 13.

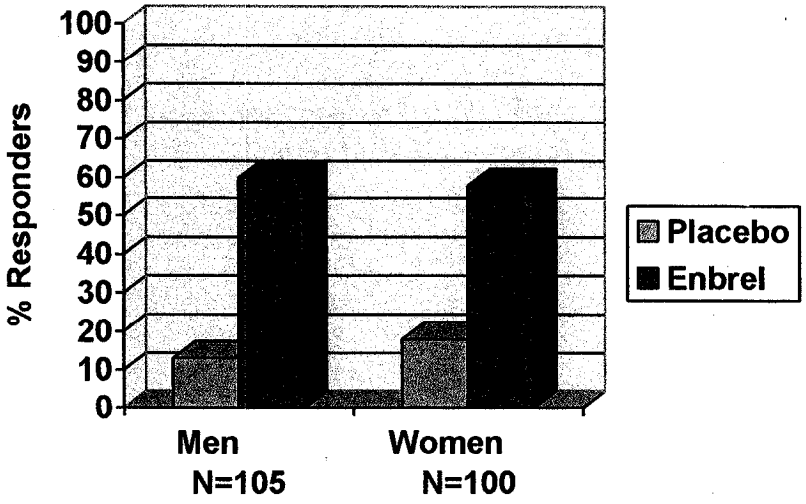

Figure 1: ACR20 responses, subsetted by gender

A variety of baseline disease characteristics could influence the likelihood of clinical responses, including concomitant anti-rheumatic medications and baseline activity of disease. Similar higher response rates were observed among etanercept-treated patients than controls among the roughly half of patients who were taking concomitant MTX and among those who were not (**Figure 2**). When patients were subsetted based on an elevated CRP level at baseline, higher response rates were observed both among patients with a baseline CRP level of 2 or higher as well as among the patients with lower levels or CRP. Of note, the likelihood of response was higher for patients with elevated CRP levels (76%) than those with lower levels (45%) (**Figure 3**). Similar rates of response to etanercept were observed in patients subsetted based on the following baseline disease characteristics (**Figure 4**, **Figure 5** and **Figure 6**):

- Patients with higher vs. lower levels of disability at baseline

- Patients with higher vs. lower baseline tender joint counts
- Patients with longer or shorter disease duration at baseline

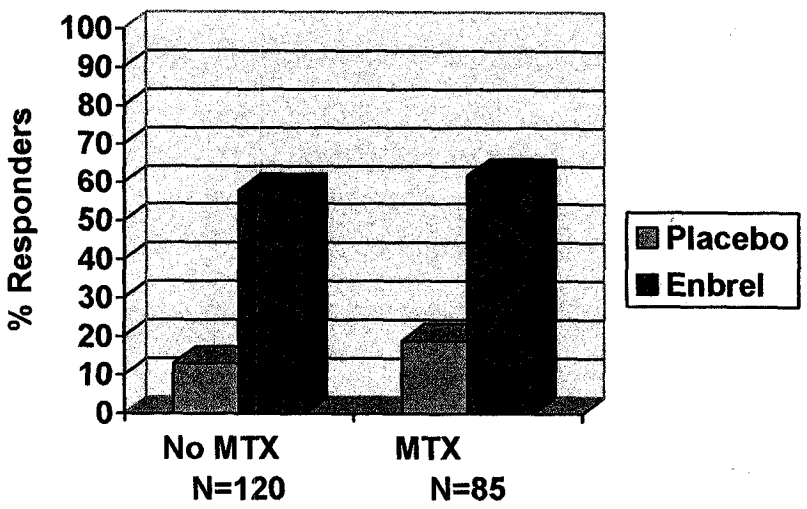

Figure 2: ACR20 responses, subsetted by concomitant MTX use

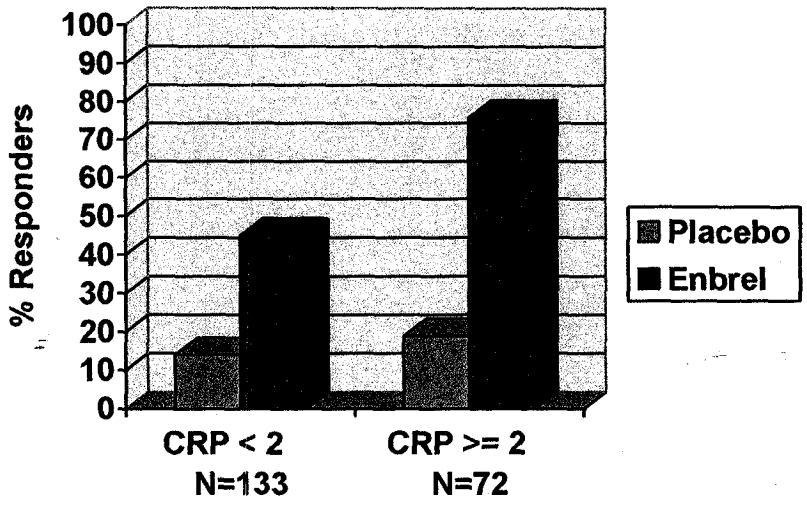

Figure 3: ACR20 responses, subsetted by baseline CRP levels

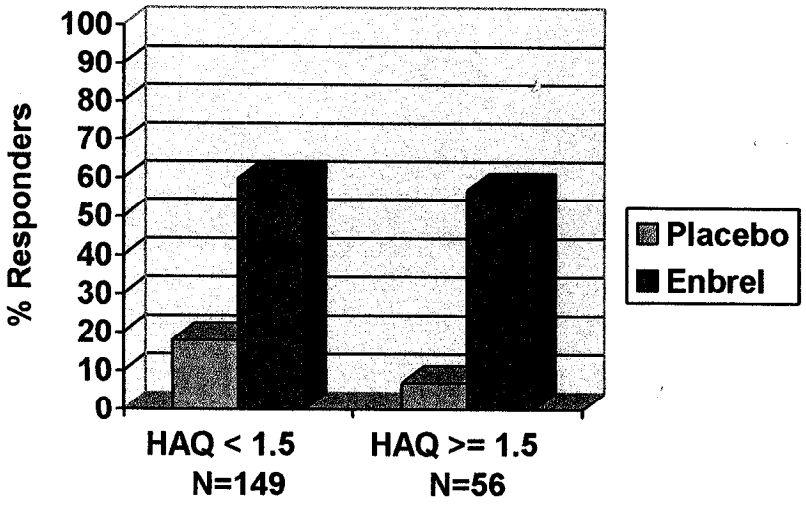

Figure 4: ACR20 responses, subsetted by baseline HAQ scores

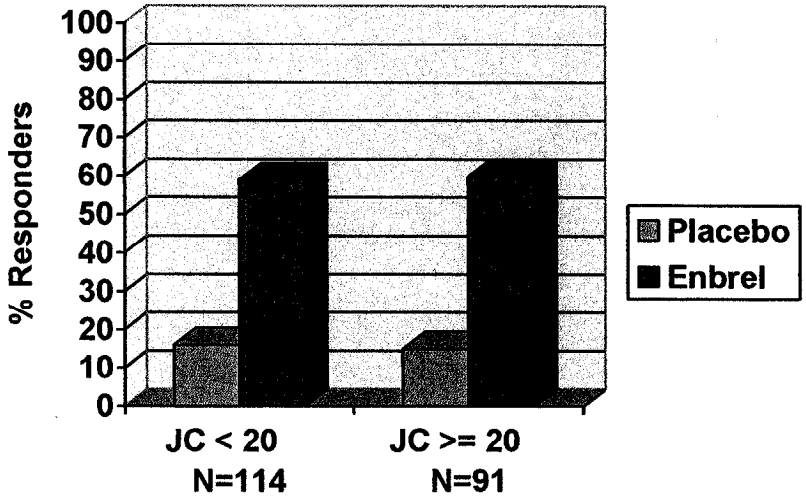

Figure 5: ACR20 responses, subsetted by baseline tender joint count

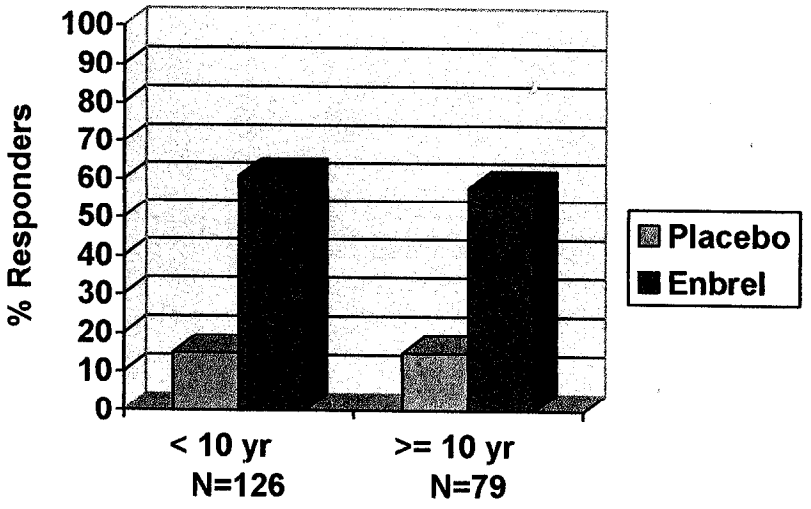

Figure 6: ACR20 responses, subsetted by baseline duration of disease

Side effects that occur more commonly with active study drug than with control can be a source of unblinding, potentially leading to bias in a clinical trial. Injection site reactions (ISR's) have been associated with use of etanercept and were seen in 36% of etanercept-treated patients in this trial compared to 9% in controls. To assess whether the occurrence of ISR's in the etanercept group may have influenced the outcomes, ACR20 responses were assessed in patients subsetted by the presence or absence of ISR's. As shown in **Figure** 7, responses in the etanercept and control groups were observed at a similar frequency in the group free of ISR's as in the group experiencing ISR's.

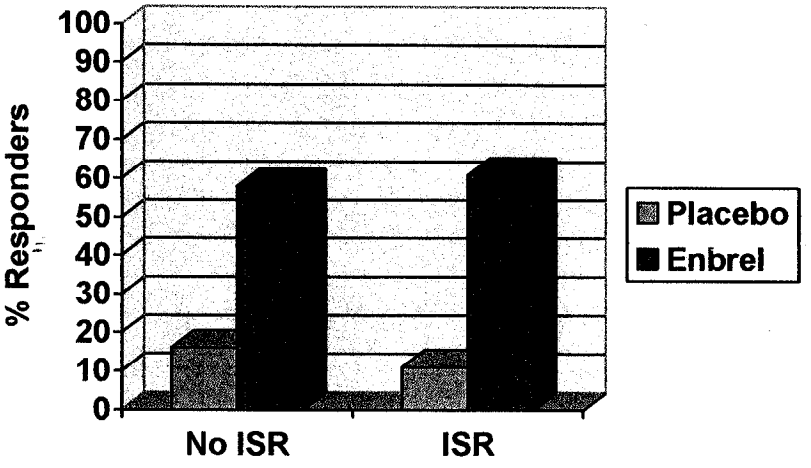

Figure 7: ACR20 responses, subsetted by presence of injection site reactions (ISR's). 65 etanercept-treated patients had no ISR, while 36 did. 95 placebo-treated patients had no ISR, while 9 did.

2. *Other outcome measures*

Health-related quality of life (HRQL) was measured using the SF-36 (Table 11). The eight subdomains were combined into 2 summary scores, the mental summary score (MCS) and the physical summary score (PCS). For both the MCS and PCS, scores of 50 represent norms for the US population and a 10-point difference represents one standard deviation. Baseline scores for the PCS and MCS were similar in the etanercept and control groups. Baseline PCS scores were clearly lower than US norms, by approximately one-and-one-half standard deviations. Improvement in the PCS was observed as early as week 4 and was maintained out to 6 months. No improvement in PCS was observed in the placebo-treated group.

In contrast to the findings with the PCS, baseline MCS scores were not below US norms at baseline. In fact, the median MCS scores for both groups slightly exceeded US norms at baseline. The fact that MCS scores were not depressed at baseline limits the ability of this measure to show improvement in the trial. No change in the mean MCS scores was observed in the placebo group. Trends toward higher MCS scores were observed in the etanercept-treated group at 4, 12 and 24 weeks.

To explore the distribution of improvements in SF-36 scores, patients were assessed based on whether they experienced a 5 or 10 unit improvement in their PCS or MCS scores (Table 12). Improvements of 5 units or greater at 6 months in the PCS were observed in 20% of controls and approximately 60% of etanercept-treated patients. Improvements of 10 units or greater at 6 months in the PCS were seen in 9% of controls and 43% of etanercept-treated patients. The proportion of patients with 5 or 10 unit improvements in the MCS was numerically higher in the etanercept-treated patients, but the results were not statistically significant.

Table 11: SF-36 Scores

	Physical Component Summary (PCS)**			**Mental Component Summary (MCS)****		
Parameter	Placebo N = 104 mean (median)	Etanercept N = 101 mean (median)	p value*	Placebo N = 104 mean (median)	Etanercept N = 101 mean (median)	p value*
Actual values: †						
Baseline	35.7 (34.8)	35.8 (36.1)		48.4 (51.2)	50.9 (53.8)	
4 weeks	36.2 (35.4)	41.7 (43.8)		50.1 (52.9)	53.2 (55.6)	
12 weeks	37.0 (36.8)	44.7 (48.3)		49.2 (53.7)	53.3 (55.4)	
24 weeks	36.4 (35.9)	45.1 (48.2)		48.4 (51.0)	53.6 (55.1)	
Change from baseline:						
4 weeks	0.5 (0.7)	5.8 (5.1)	< 0.001	1.7 (0.9)	2.3 (0.9)	0.748
12 weeks	1.2 (1.6)	8.9 (6.8)	< 0.001	0.8 (0.3)	2.3 (1.0)	0.392
24 weeks	0.7 (0.5)	9.3 (7.7)	< 0.001	-0.1 (-0.1)	2.7 (1.1)	0.062

* p values determined by 2-sided Wilcoxon rank sum test

**0 = worst; 100 = best; 50 = US norm

Table 12: Patients with at least 5 or 10 Unit Improvements in SF-36

	Physical Component Summary (PCS)			**Mental Component Summary (MCS)**		
Parameter	Placebo N = 104 n (%)	Etanercept N = 101 n (%)	p value*	Placebo N = 104 n (%)	Etanercept N = 101 n (%)	p value*
≥ 5 unit improvement						
4 weeks	19 (18)	51 (50)	< 0.001	27 (26)	27 (27)	0.903
12 weeks	28 (27)	59 (58)	< 0.001	20 (19)	28 (29)	0.152
24 weeks	21 (20)	62 (61)	< 0.001	19 (18)	27 (27)	0.148
≥ 10 unit improvement						
4 weeks	4 (4)	27 (27)	< 0.001	14 (13)	14 (14)	0.931
12 weeks	10 (10)	42 (42)	< 0.001	14 (13)	16 (16)	0.629
24 weeks	9 (9)	43 (43)	< 0.001	12 (12)	20 (20)	0.104

* p values determined by Cochran-Mantel-haenszel row means test

The SF-36 is made up of 8 subdomains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. The MCS and PCS are summary scores that are calculated based on the results of the individual subdomains. Improvements in the subdomains physical function, physical role, bodily pain, general health and vitality contribute positively to the PCS, while improvements in social functioning, role emotional and mental health subdomains contribute negatively. Conversely, improvements in vitality, social functioning, role emotional and mental health contribute positively to the MCS, while improvements in physical function, physical role, bodily pain, general health contribute negatively.

The results of the individual subdomains of the SF-36 at baseline and 6 months are shown in Table 13. No major imbalances were apparent at baseline in any of the individual subdomains. Small (all less than 2 units) and inconsistent changes in the subdomains were observed in the placebo group. Treatment with etanercept was associated with improvements in each of the subdomains at 6 months. The comparison to placebo was statistically significantly higher for all subdomains, with the exception of emotional role where a trend to improvement was observed, but the result was not statistically significant.